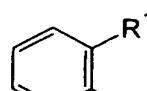
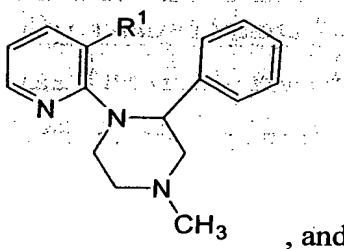
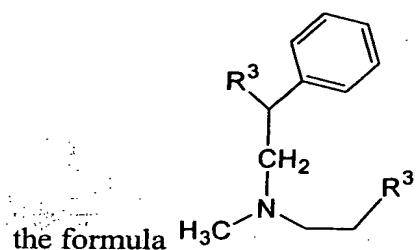


WE CLAIM:

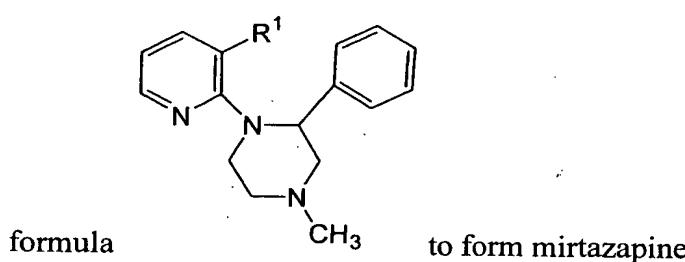
1. A method for the preparation of mirtazapine, comprising the steps of:

(a) reacting a compound of the formula  with a compound of



to form a compound of the formula

(b) adding a ring closing reagent to the compound of the



wherein R¹ is selected from the group consisting of hydroxymethyl, chloromethyl, bromomethyl and iodomethyl; R² is amine; and R³ is selected from the group consisting of chloro, fluoro, bromo and iodo.

2. The method of claim 1, wherein R¹ is hydroxymethyl, R² is -NH₂, and R³ is chloro.

3. The method of claim 1, wherein said a ring closing reagent is selected from the group consisting of sulfuric acid, concentrated sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid, phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide, Lewis acids, aluminum chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

4. The method of claim 2, wherein said ring closing reagent is sulfuric acid.

5. The method of claim 1 which further comprises the step of heating.

6. A method for the preparation of mirtazapine, comprising the steps of:

(a) reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine, and

(b) adding a ring closing reagent to the 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine to form mirtazapine.

7. The method of claim 6, wherein said a ring closing reagent is selected from the group consisting of sulfuric acid, concentrated sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid, phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide, Lewis acids, aluminum chloride, ferric chloride,

zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

8. The method of claim 6 wherein the ring closing reagent is sulfuric acid.

9. The method of claim 6 further comprising the step of heating.

10. A process for making 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine comprising the step of reacting 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base wherein the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

11. The process of claim 10 wherein the ratio of the base to 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is about 12 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine to about 9 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

12. The process of claim 10 wherein the base is potassium hydroxide or sodium hydroxide

13. The process of claim 12 wherein the mixture of the 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine and the base is heated to at least about 130°C.

14. The process of claim 13 wherein the mixture is heated to about 130°C to about 150°C.

15. The process of claim 12 wherein the hydrolysis is carried out in water and an aprotic polar solvent.

16. The process of claim 12 wherein the hydrolysis is carried out in a mixture of water and a solvent selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, dimethylformamide, dimethylacetamide and dimethylsulfoxide.

17. The process of claim 12 wherein the hydrolysis is carried out at a pressure of about 3 to about 4 atmospheres pressure.

18. The process of claim 12 wherein the hydrolysis is carried out at almost neat conditions.

19. A process for recrystallized mirtazapine from crude mirtazapine comprising the steps of:

- (a) heating a mixture of crude mirtazapine and a solvent;
- (b) cooling the mixture such that purified mirtazapine precipitates; and
- (c) isolating the recrystallized mirtazapine.

20. The process of claim 19 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, acetone, and mixtures thereof.

21. The process of claim 20 further comprising the step of adding water to the mixture of mirtazapine and solvent to facilitate precipitation of mirtazapine.

22. The process of claim 19 wherein the solvent is selected from the group consisting of toluene, hexane, and methylene chloride, and mixtures thereof.

23. The process of claim 20 wherein the solvent is ethanol.

24. The process of claim 19 wherein the recrystallized mirtazapine is a mirtazapine water adduct.

25. The product of the process claim 24.

26. Mirtazapine prepared according to the process of claim 1.

27. A pharmaceutical composition comprising a therapeutically effective amount of mirtazapine of claim 26, and a pharmaceutically acceptable carrier.

28. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 27.